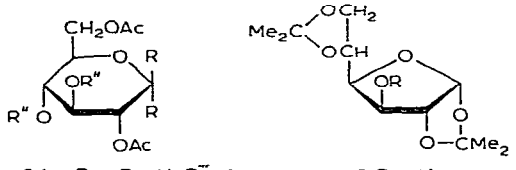
Note

Improved preparations of 1,2,3,6- and 1,2,4,6-tetra-*O*-acetyl-β-D-glucopyranose

B H KOEPPEN
Department of Food Science, University of Stellenbosch, Stellenbosch (South Africa)
(Received November 12th, 1971, accepted for publication, January 24th, 1972)

Tetra-*O*-acetyl-D-glucopyranoses are useful intermediates in the synthesis of glycosyl-D-glucoses The β-D tetra-acetate is usually preferred for Koenigs–Knorr syntheses because the resulting β-D peracetates usually crystallize more readily than the α-D anomers[1–5]

Of the known tetra-*O*-acetyl-D-glucopyranoses, 1,2,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**1**) is the least accessible It is obtained[6] by benzylation of 1,2 5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**), followed by acid hydrolysis and acetylation, and hydrogenolysis of the resulting 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranose (**5**) The overall yield of **1** from **2** was 13 7%, the lowest-yielding stage[7] (48 3%) being **2**→**3** The optimisation of each step is now reported



1 R = OAc, R = R = H, R‴ = Ac
5 R = OAc R′ = H R″ = CH_2Ph, R‴ = Ac
6 R = R′ = H, R = OAc R‴ = Ac
7 R = OAc, R = R″ = H R‴ = Ac

2 R = H
3 R = CH_2Ph

4

T l c revealed that benzylation of **2** was incomplete by the method of Freudenberg *et al* [7], or modifications thereof[8,9], whereas the reaction occurred quantitatively within 30 min when the method of Zemplén *et al* [10], as applied to **2** by Adams and co-workers[11], was employed On hydrolysis of **3** by Freudenberg's method[7,11], rapid hydrolysis of the 5,6-*O*-isopropylidene group occurred but removal of the more stable 1,2-*O*-isopropylidene group was incomplete The prolonged acid treatment required for complete hydrolysis caused partial degradation of the product **4** (t l c) Hence, a two-stage hydrolysis was used which gave >75% overall yields of **4** (*cf* 50.6%, ref. 11)

By slight modification of the conditions[6] for the acetylation of **4**, the reaction time was reduced from 48 h to 15 min, with retention of a high yield of acetate **5**.

The hydrogenolysis stage 5→1 proceeded efficiently in acetone solution, from which **1** could be recovered more conveniently than from acetic acid[6] Similarly, the non-crystalline 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-α-D-glucopyranose (formed in ~20% yield on acetylation of **4**) gave crystalline 1,2,4,6-tetra-*O*-acetyl-α-D-glucopyranose (**6**), hitherto unknown

The optimised synthesis gave a 55 5% overall yield of **1** from **2**, and was considerably less time-consuming than the original procedure

Attempts to prepare 3-*O*-glycosyl-D-glucoses by condensing **2** with acetylated glycosyl halides, under the conditions of Helferich and Zirner[2], resulted in acetal migration and formation mainly of 6-*O*-(*O*-acetylglycosyl)-1,2 3,5-di-*O*-isopropylidene-α-D-glucofuranoses[12] Other attempts to glycosylate **2** under Koenigs–Knorr conditions[13–15] and by the orthoester method[16] have yielded similar results, although a successful synthesis of laminaribiose by a modified orthoester method has been reported recently[16]

Previously, 1,2,3,6-tetra-*O*-acetyl-β-D-glucopyranose (**7**) has been prepared[17–19] from the 1,2,3,4-tetra-acetate by acetyl migration, in overall yields of 10–15% from D-glucose, with the conversion 1,2,3,4-tetra-acetate→**7** being <50% efficient [17] Recently, difficulties have also been reported in effecting the acetyl migration[20]

In a simplified preparation of **7**, D-glucose was converted quantitatively into the 6-*O*-trityl derivative which was then acetylated Treatment of the resulting 1,2,3,4-tetra-*O*-acetyl-6-*O*-trityl-αβ-D-glucoyranose in sequence with hydrogen bromide–acetic acid and mercuric acetate gave **7** 2,3,6-Tri-*O*-acetyl-α-D-glucopyranosyl bromide is a probable intermediate in this reaction sequence Although the yield of **7** is critically dependent on the hydrogen bromide treatment and careful control of the reaction conditions is necessary, consistent overall yields of 38–40% of **7** from D-glucose were obtained

EXPERIMENTAL

General — Thin-layer chromatography (t l c) was performed on Merck Kieselgel G, using acetone–benzene mixtures, with sulphuric acid as spray reagent For preparative t l c, glass plates (20 × 30 cm) were used, zones were located with u v light (366 nm), and components were eluted with acetone Evaporations were carried out under diminished pressure I r spectra were recorded on a Beckman IR9 spectrophotometer by the potassium bromide disc method, band intensities are indicated m, moderate, s, strong, w, weak N m r spectra were measured on a Varian HA-60IL spectrometer with chloroform-*d* as solvent, and tetramethylsilane as internal standard Melting points are uncorrected, and were determined by the Kofler method

1,2,4,6-Tetra-O-acetyl-β-D-glucopyranose (**1**) — A solution of 1,2 5,6-di-*O*-isopropylidene-α-D-glucofuranose[21] (**2**, 10 g) in benzyl chloride (50 ml) was stirred vigorously at 100°, and dry, powdered potassium hydroxide (26 g) was added slowly After 30 min, the mixture was cooled, diluted with water (200 ml), and extracted with

chloroform (3 × 50 ml) The combined extracts were washed with water and then evaporated, and a solution of the residue in a mixture of ethanol (30 ml) and 0 8 M hydrochloric acid (10 ml) was boiled for 15 min The cooled solution was neutralized with Amberlite CG-45 (Type I, OH^-) resin (20 g) which was washed with ethanol (500 ml) The combined solution and washings were evaporated to dryness, and the residue (10 6 g) was crystallized from ethyl acetate (~30 ml) to yield 3-*O*-benzyl-D-glucose (**4**, 4 53 g), m p 132–134° A solution of the residue from the mother liquors in a mixture of ethanol (15 ml) and 0 8M hydrochloric acid (5 ml) was maintained at 55° for 15 h, or until t l c (acetone–benzene, 3 2) revealed only a trace of residual 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose After neutralization and evaporation, crystallization of the residue (6 3 g) from ethyl acetate (~15 ml) afforded additional **4** (2 82 g), m p 132–134° Purification of the mother liquor by t l c (25 plates, acetone–benzene, 3 2) gave a further 0 70 g, m.p 131–133°, total yield 8 05 g (77 5%).

A solution of **4** (8 05 g) in acetic anhydride (35 ml) and pyridine (35 ml) was heated nearly to boiling, and then left at room temperature for 15 min The product, isolated in the usual way, was crystallized from ethanol to yield 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranose (**5**, 9 63 g, 73 7%), m p 105–107°

Hydrogenolysis of a solution of **5** (9 62 g) in acetone (70 ml) over 10% palladium-on-carbon (1 5 g), with crystallization of the product from dichloromethane–ether, gave **1** (7.43 g, 97 2%, overall yield from **2**, 55 5%), m p 126–127° $[\alpha]_D^{18}$ −13 6° (*c* 2 5, chloroform), lit [6] m p 127°, $[\alpha]_D^{20}$ −13 5° (chloroform)

With toluene-*p*-sulphonyl chloride–pyridine, in the usual manner, **1** gave the 3-toluene-*p*-sulphonate (97 1%), m p 174–176° (dec , from ethanol), $[\alpha]_D^{21}$ +13 5° (*c* 3 24, tetrachloroethane), lit [6,22] m p 174–176°, $[\alpha]_D$ +13 7° (tetrachloroethane)

1,2,4,6-Tetra-O-*acetyl*-α-D-*glucopyranose* (**6**) — After evaporation of the mother liquor from the above crystallization of **5**, hydrogenolysis of a solution of the residue (2 g) in methanol (15 ml) over 10% palladium-on-carbon (0 6 g) afforded a product which crystallized from dichloromethane–ether to give **6** (0 78 g, 5 8% overall yield from **2**), m p 161–163°, $[\alpha]_D^{21}$ +87 9° (*c* 2 89, chloroform), ν_{max}^{KBr} 3470m, 1755s, 1640w, 1437w, 1380m, 1243s, 1155m, 1112w, 1080m, 1042s, 982w, 940m, 748w, 700w, 608w, 552w, 493w cm^{-1} N m r data τ 3 70 (doublet, $J_{1,2}$ 3 5 Hz, H-1), 4 98 (triplet, $J_{3,4} = J_{4,5}$ 9 5 Hz, H-4), 5 01 (quartet, $J_{1,2}$ 3 5 Hz, $J_{2,3}$ 10 0 Hz, H-2), 5 87 (multiplet, H-3, H-5, H-6a, H-6b), 6 87 (broad singlet, HO-3), 7 84, 7 88, 7 92 (singlets, 12 protons, intensity ratio 1 1 2, 4 × OAc)

Anal. Calc for $C_{14}H_{20}O_{10}$ C, 48 3, H, 5 7, OAc, 49 4. Found C, 48 5, H, 5 7, OAc, 49 2

Acetylation of **6** with acetic anhydride–pyridine at 100° gave penta-*O*-acetyl-α-D-glucopyranose (89 5% from ethanol), m p and mixed m p 112–113°

Attempts to prepare a crystalline 3-toluene-*p*-sulphonate were unsuccessful, but with methanesulphonyl chloride–pyridine, in the usual way, **6** gave the 3-methanesulphonate (90 3% from ethanol), m p 169–170°, $[\alpha]_D^{23}$ +82 8° (*c* 3 68, chloroform)

Anal Calc for $C_{15}H_{22}O_{12}S$ C, 42 3, H, 5 2, S, 7 5 Found C, 42 1, H, 5 1, S, 7 6

1,2,3,6-Tetra-O-acetyl-β-D-glucopyranose (7) — Anhydrous D-glucose (10 g) and trityl chloride (16 3 g) were stirred with anhydrous pyridine (40 ml) at 25° for 2 h The mixture was then heated nearly to boiling and cooled, and additional trityl chloride (8 g) and pyridine (20 ml) were added After stirring for a further 2 h, when t l c (acetone–benzene, 3 2) revealed the formation of 6-*O*-trityl-D-glucose to be complete, acetic anhydride (60 ml) was added, and the solution was heated nearly to boiling and then left at room temperature for 30 min Conventional isolation by chloroform extraction gave a crude product (40 8 g) which was dissolved in dichloromethane (30 ml) and treated with a solution of 40% hydrogen bromide in glacial acetic acid (70 ml) at 20° After exactly 2 5 min, and, within 2 min, the precipitated trityl bromide was collected and washed with acetic acid, and the combined filtrate and washings were diluted with chloroform (150 ml) and extracted with iced water

The chloroform solution was washed with saturated, aqueous sodium hydrogen carbonate and water until the washings were neutral to litmus, and was then filtered through anhydrous sodium sulphate and evaporated to dryness at 35°. The residue was dissolved in a solution of mercuric acetate (25 g) in glacial acetic acid (100 ml) After 30 min at room temperature, the solution was diluted with chloroform (250 ml), washed with water (4 × 100 ml), and evaporated to dryness Crystallization of the residue from benzene (~35 ml) afforded **7** (6 92 g) After fractionation of the mother liquor by t l c (30 plates, acetone–benzene, 6 94), an additional 0 93 g was obtained, total yield of **7**, 7 85 g (40 6%), m p 131–133°, $[\alpha]_D^{23}$ −32 2° (*c* 3 07, chloroform), lit [17,18] m p 132–134°, $[\alpha]_D^{20}$ −33 0° (chloroform)

Under conditions which resulted in the quantitative formation of 6-*O*-trityl-D-glucose from D-glucose, t l c (acetone–benzene, 1 4) revealed that **7** remained unchanged, even after 24 h However, with toluene-*p*-sulphonyl chloride–pyridine, in the usual manner, **7** gave the 4-toluene-*p*-sulphonate (88 5% from ether), m p 111–113°, $[\alpha]_D^{21}$ −16 1° (*c* 2 64, chloroform), lit [18] m p 111–112°, $[\alpha]_D^{20}$ −15 9° (chloroform)

ACKNOWLEDGMENTS

The author is indebted to Mr P de K du Preez for technical assistance, and to Mr H S C Spies, Department of Chemistry, University of Stellenbosch, for recording the n m r spectra

REFERENCES

1 D D Reynolds and W L Evans, *J Amer Chem Soc*, 60 (1938) 2559
2 B Helferich and J Zirner, *Ber*, 95 (1962) 2604
3 R. U Lemieux and G Huber, *Can J Chem*, 31 (1953) 1040
4 B H Koeppen, *Carbohyd Res*, 7 (1968) 410
5 B H Koeppen, *Tetrahedron*, 24 (1968) 4963
6 K Freudenberg and E Plankenhorn, *Ann*, 536 (1938) 257
7 K Freudenberg, H von Hochstetter, and H Engels, *Ber*, 58 (1925) 666
8 C M McCloskey, *Advan Carbohyd Chem*, 12 (1957) 137
9 A S Meyer and T Reichstein, *Helv Chim Acta*, 29 (1946) 152
10 G Zemplen, Z Csuros, and S Angyal, *Ber*, 70 (1937) 1848

11 M H ADAMS, R E REEVES, AND W F GOEBEL, *J Biol Chem*, 140 (1941) 653
12 B H KOEPPEN, unpublished results
13 K FREUDENBERG AND K VON OERTZEN, *Ann*, 574 (1951) 37
14 P BACHLI AND E G V PERCIVAL, *J Chem Soc*, (1952) 1243
15 K MATSUDA, *Chem Ind (London)*, (1958) 1627
16 N. K. KOCHETKOV, A F BOCHKOV, T A SOKOLOVSKAYA, AND V J SNYATKOVA, *Carbohyd Res*, 16 (1971) 17
17 B HELFERICH AND W KLEIN, *Ann*, 455 (1927) 173
18 B HELFERICH AND W KLEIN, *Ann*, 450 (1926) 219
19 D D REYNOLDS AND W. L EVANS, *Org Syn Coll Vol*, 3 (1955) 432
20 A NOWAKOWSKI AND Z MROCZKOWSKI, *Rocz Technol Chem Zywn*, 15 (1969) 37, *Chem Abstr*, 73 (1970) 4147h
21 O TH SCHMIDT, *Methods Carbohyd Chem*, 2 (1963) 318
22 K FREUDENBERG AND O IVERS, *Ber*, 55 (1922) 929.